REMARKS/ARGUMENTS

Applicants respectfully request reconsideration of the instant claims in light of the amendments and remarks presented herein.

Claims 1-14 were pending in this application. Claims 1, 5, 7 and 10 have been amended and claims 3, 4, 6, 8 and 9 have been canceled. Claim 14 was amended to correct a typographical error. New claims 15 and 16 have been added. New claims 15 and 16 find support in canceled claim 3 and in the specification in paragraph 0064. No new matter has been introduced as a result of the claim amendments.

Claim Objections

Claims 3-4 have been canceled and claim 10 has been amended such that the abbreviation α-Me-MSO refers to alpha-methyl-D,L-methionine-SR-sulfoxamine and the abbreviation α-Et-MSO refers to alpha-ethyl-D,L-methionine-SR-sulfoxamine. The abbreviations have been removed from claim 10. Claims 11-13 depend from amended claim 5. Applicants respectfully request the objections to claims 10 and 11-13 be withdrawn in light of the claim amendments. New claims 15 and 16 are in agreement with these amendments.

Regarding the use of the abbreviations α-Me-MSO and α-Et-MSO in the specification, these abbreviations refer to alpha-methyl-D,L-methionine-SR-sulfoxamine and alpha-ethyl-D,L-methionine-SR-sulfoxamine, respectfully, wherein the abbreviation refers to compositions containing a mixture of the 4 isomers.

Double Patenting – 35 U.S.C. §101

Claims 1-14 are provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 1-14 of co-pending Application No. 10/715,679. Applicant has expressly abandoned co-pending application 10/715,679 and a copy of the filed Express Abandonment is attached hereto.

Claims 1-14 are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,013,660 in view of

Griffith OW et al. (Journal of Biological Chemistry 254:1205, 1979). Claims 3, 4, 6, 8 and 9 have been canceled.

For the reasons discussed below, Applicants traverse the obviousness-type double patent rejection over U.S. Patent 6,013,660 in view of Griffith et al. As correctly characterized by the Examiner, the policy behind the judicially-created doctrine of obviousness-type double patenting is "to prevent the unjustified or improper timewise extension of the 'right to exclude' granted by a patent." However, the Applicants respectfully submit that allowance of the Applicants' pending claims 1, 2, 5, 7, 10-16 would clearly not lead to an improper timewise extension of the claims in U.S. Patent 6,013,660.

Claims 1 and 2 of the '660 patent cover a method of treating mammalian disease associated with infection by pathogenic mycobacterium comprising administering L-methionine-S-sulfoximine to the mammal. Pending and amended claims 1 and 2 of the instant application cover compositions comprising a mycobacterial glutamine synthetase inhibitor of a genus that does not include L-methionine-S-sulfoximine. Furthermore, because claims 1 and 2 of the '660 patent are method of use claims, Applicants respectfully submit that claims 1 and 2 of the instant application are not just obvious variations of method of use claims 1 and 2 of the '660 patent that would extend the patent term of the '660 patent.

Regarding claims 5, 7 and 10-16, the Examiner states that the '660 patent does not expressly disclose alpha-alkylated L-methionine-S-sulfoximine or a racemic mixture of the same or other alpha-alkylated butyrates for the treatment of pathogenic mycobacterium infection. The genus of compounds recited in amended claim 5 of the instant application does not include L-methionine-S-sulfoximine. The Examiner states on page 5 of the Office Action of August 4, 2006 that "Griffith et al. discloses the use of alpha-alkylated analogs of methionine sulfoximine, in particular alpha-ethyl-methionine sulfoximine for the selective inhibition of glutamine synthetase." Applicant respectfully points out that the glutamine synthetase (GS) used in Griffith et al. is mammalian GS which is a different protein than mycobacterial GS. As is known to persons of ordinary skill in the art, mycobacterial GS are dodecamers comprised of two face-to-face

hexameric rings of subunits and are regulated by adenylation. Mammalian GS are octamers rather than dodecamers, are of lower molecular weight, and are not regulated by adenylation. The properties and regulation of mammalian GS and mycobacterial GS are therefore different and variable and a person of ordinary skill in the art would recognize that their susceptibility to inhibitors can vary significantly. Applicants draw the examiner's attention to paragraphs 0038 and 0039 of the instant specification for a discussion of the differences between mammalian GS and mycobacterial GS. Therefore, alpha-alkylated methionine sulfoximines were not known to even inhibit mycobacterial GS and certainly not known to cause selective inhibition of mycobacterial GS *in vivo* before the invention recited in the instant claims.

Thus, the methods recited in claims 1 and 2 of the '660 patent do not read on the methods recited in claims 5, 7 and 10-16 of the instant application in view of the disclosure of Griffith et al. Additionally, there is nothing in the art that teaches or suggests that the methods covered by the Applicants' claims are equivalent to the methods covered by the claims of the '660 patent, which would allow the Applicants to make a claim that someone using the methods covered by the '660 patent in view of Griffith et al. would be infringing the Applicants' claims. Moreover, the Applicants' claims are not just obvious variations of claims 1 and 2 of the '660 patent that would extend the patent term of the '660 patent.

Rejections – 35 U.S.C. §112

Claims 5-6 and 11-13 stand rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the disclosed compounds of Formula I, does not reasonably provide enablement for all gamma-substituted alpha-amino-alpha-alkyl-butyrates.

Claim 5 has been amended to incorporate the compounds recited in claim 1. Claim 7 has been amended to correct dependency accordingly. Therefore the method of the claim 5 comprises anti-mycobacterial compositions according to Formula 1 wherein the anti-mycobacterial compositions effectively inhibit mycobacterial glutamine synthetase (MbGS), but do not substantially interfere with mammalian glutamine

synthetase (MGS) *in vivo* such that said mycobacterial infection is treated, palliated or inhibited.

In light of the claim amendments and the Examiner's statement that the compounds of Formula 1 are enabled, Applicants respectfully assert that this rejection of pending and amended claims 5 and 11-13 under 35 U.S.C. §112, first paragraph be withdrawn.

Claims 1-13 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants have amended claim 1 to remove the phrase "wherein said anti-mycobacterial composition effectively inhibits MbGS but does not substantially inhibit mammalian glutamine synthetase (MGS) in vivo." Claims 3 and 4 have been canceled.

Claims 5 and 10 have been amended, in part, to recite "wherein said composition effectively inhibits mycobacterial glutamine synthetase (MbGS), but does not substantially interfere with mammalian glutamine synthetase (MGS) *in vivo* in an anti-mycobacterial effective amount."

New claim 15 incorporates the amended language of claims 5 and 10.

Therefore, Applicants respectfully assert that pending and amended claims 1, 2, 5, 7 and 10-13 and new claims 15 and 16 in light of the disclosure in the specification, are not indefinite and request that the Examiner withdraw the 35 U.S.C. §112, second paragraph rejection of these claims.

Rejections – 35 U.S.C. §102

A claim is anticipated under 35 U.S.C. §102 only if each and every element as set forth in a claim is found, either expressly or inherently described, in a single prior art reference (MPEP §2131; *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d, 628, 631, 2 USPQ2d 1051 (Fed. Cir. 1987)).

Claims 1-4 stand rejected under 35 U.S.C. §102(b) as being anticipated by Griffith et al. (Journal of Biological Chemistry 253:2333-2338, 1978, hereinafter "Griffith

1978" or Methods in Enzymology 143:286-291, 1987, hereinafter "Griffith 1987"). Claims 3 and 4 have been canceled and claim 1 has been amended.

Griffith 1978 discloses alpha-methyl-D,L-methionine-SR-sulfoximine and alpha-ethyl-D,L-methionine-SR-sulfoximine as inhibitors of mammalian glutamine synthetase (GS) and as inducing convulsions.

Griffith 1987 discloses the synthesis of alpha-ethyl-D,L-methionine-SR-sulfoximine.

Independent claims 3 and 4 have been canceled. Independent claim 1 has been amended to recite, in part, "if R_2 is methyl sulfoximine, R_1 is not methyl or ethyl." Claim 1 therefore does not claim the compounds of Griffith 1978 or Griffith 1987.

Therefore, Applicants respectfully assert that pending and amended claims 1 and 2 are not anticipated by Griffith 1978 or Griffith 1987 and request that the Examiner withdraw the rejection of claims 1 and 2 under 35 U.S.C. §102(b) over Griffith et al.

Claim 1 is further rejected under 35 U.S.C. §102(b) as being anticipated by Lejczak et al. (Experimentia 37:461, 1981).

Lejczak et al. discloses phosphonic analogues of glutamic acid and glutamine. The compounds of Lejczak inhibit rat liver glutamine synthetase. Lejczak does not disclose inhibition of mycobacterial glutamine synthetase.

Independent claim 1 has been amended to recite, in part, "if R_2 is phosphonate, R_1 is not methyl; if R_2 is phosphinate, R_1 is not methyl." Claim 1 therefore does not claim the compounds of Lejczak.

Therefore, Applicants respectfully assert that amended claim 1 is not anticipated by Lejczak and request that the Examiner withdraw the rejection of claim 1 under 35 U.S.C. §102(b) over Lejczak et al.

Rejections – 35 U.S.C. §103

To reject a claim under 35 USC §103(a), the Examiner bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. See *In re Bell*, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1992). If the Examiner cannot establish a *prima facie* case

of unpatentability, then without more the applicant is entitled to grant of the patent. See *In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed Cir. 1992). The Examiner must meet a three-part test to render a claimed invention *prima facie* obvious.

To begin with, the prior art references cited by the Examiner must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the application." See *In re Kotzab*, 55 U.S.P.Q.2d 1316 (Fed. Cir. 2000). Where one reference is relied upon by the Examiner, there must be a suggestion or motivation to modify the teachings of that reference. *See id.* Where an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. See *WMS Gaming Inc. v. International Game Technology*, 51 U.S.P.Q.2d 1386 (Fed. Cir. 1999). The suggestion may be found in implicit or explicit teachings within the references themselves, from the ordinary knowledge of one skilled in the art, or from the nature of the problems to be solved. *See id.*

Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. See *In re Dow Chemical*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). The expectation of success, like the motivation to combine two prior art references, must come from the prior art, not the applicant's disclosure. *See id.*

Finally, the Examiner must demonstrate that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims, See *In re Gartside*, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000).

If any one of these three factors is not met, the PTO has failed to establish a prima facie case of obviousness and the applicant is entitled to grant of a patent without making any affirmative showing of non-obviousness.

Claims 1-14 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Harth et al. (J. Exp. Med. 189:1425, 1999) in view of Griffith et al. (Methods in Enzymology 143:286, 1987). Claims 3, 4, 6, 8 and 9 have been canceled. Claims 1, 5, 7 and 10 have been amended as discussed *supra*.

Harth et al. disclose L-methionine-S-sulfoximine as an inhibitor of mycobacterial GS and its ability to block growth of pathogenic mycobacteria in human monocytes. Harth et al. does not disclose the alpha-alkylated compounds of formula 1.

Griffith et al. discloses alpha-ethyl-methionine-sulfoximine as an inhibitor of mammalian GS. Griffith et al. does not disclose inhibitors of mycobacterial GS or use of such inhibitors as anti-mycobacterial agents.

At the time of invention of the instant claims, it was not known if the established inhibitors of mammalian GS would also inhibit mycobacterial GS. As stated *supra*, and in the specification, mammalian GS is a different protein than mycobacterial GS. Furthermore, regulation of mammalian GS and mycobacterial GS are different and variable and a person of ordinary skill in the art would recognize that their susceptibility to inhibitors can vary significantly. Therefore until the instant invention, it was not known if these claimed compounds would exhibit inhibition of mycobacterial GS to a degree sufficiently greater than their inhibition of mammalian GS. Furthermore, it was not recognized that a compound with preferentially higher inhibitory activity for mycobacterial GS over mammalian GS would be preferential for inhibiting mycobacterial growth *in vivo* and useful in the treatment, palliation and/or inhibition of mycobacterial infections.

In view of the foregoing, Applicant respectfully submits that Griffith and Harth, either alone or in combination, do not teach or suggest all the elements of the instant claims, namely anti-mycobacterial compositions and methods of treating mycobacterial infections using the compounds of formula 1 wherein the composition effectively inhibits mycobacterial GS but does not substantially inhibit mammalian GS. Furthermore, there is no expectation of success since it has been established in the prior art that mammalian GS and mycobacterial GS are substantially different proteins and compounds that have inhibitory effects on mammalian GS do not necessarily inhibit mycobacterial GS. Therefore Applicants respectfully submit that the Examiner cannot establish *prima facie* obviousness of claims 1, 2, 5, 7, 10-16. Accordingly, Applicant respectfully submits that claims 1, 2, 5, 7, 10-16 are not obvious under 35 USC §103(a)

over Harth et al. and Griffith et al. and requests the withdrawal of the outstanding rejection on this basis.

Claim 14 is rejected under 35 U.S.C. §103(a) as being unpatentable over Anderson ME (Chemico-Biological Interactions 111-112:1-14, 1998) in view of Harth et al.

Harth et al. teaches L-methionine-S-sulfoximine as an inhibitor of mycobacterial GS.

Anderson is a review of glutathione, its metabolism and modulation. Anderson teaches that L-methionine-S-sulfoximine causes convulsions. Furthermore, Anderson teaches use of ascorbate to reduce the oxidative damage cause by long-term administration of buthionine sulfoximine. Anderson does not teach or suggest use of ascorbate in combination with L-methionine-S-sulfoximine to increase the maximum tolerated dose of L-methionine-S-sulfoximine.

In view of the foregoing, Applicant respectfully submits that Anderson and Harth et al., either alone or in combination, do not teach or suggest a method of treating, palliating or inhibiting mycobacterial infections in a mammal comprising co-administering an anti-mycobacterial effective amount of L-methionine-S-sulfoximine and ascorbic acid. Furthermore, there is no expectation of success nor motivation or suggestion to combine the teachings of Harth et al. with the teachings of Anderson to achieve the claimed invention. Therefore Applicants respectfully submit that the Examiner cannot establish *prima facie* obviousness of claim 14. Accordingly, Applicant respectfully submits that claim 14 is not obvious under 35 USC §103(a) over Anderson and Harth et al. and requests the withdrawal of the outstanding rejection on this basis.

Conclusion

Applicants respectfully assert that the pending claims are in condition for allowance and request that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

Dated: 2/5/07

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